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Title: Studying the role of RNA binding proteins and RNA granules in cancer progression

During cell stress such as hypoxia, nutrient deprivation, or oxidative stress, global protein synthesis is inhibited to preserve energy via sequestration and silencing of mRNAs in RNA granules called stress granules (SGs). The latter are ribonucleoprotein complexes containing translationally inactive mRNAs, pre-initiation factors, and RNA-binding proteins that assemble in the cytoplasm under diverse cell stress conditions. On the other hand, selective translation of specific messages that reside outside of SGs allows the cell to rapidly synthesize and deploy key proteins that are needed to survive under cell stress. In this way, cells reprogram mRNA translation to adapt to or to alleviate cell stress. Y-box binding protein 1 (YB-1) is an RNA binding protein and a major translational regulator that is implicated in epithelial-to-mesenchymal transition (EMT) and metastasis. We found that YB-1 expression is markedly elevated across diverse human sarcoma sub-types, and that expression strongly correlates with poor survival in Ewing sarcoma (ES), osteosarcoma (OS), and rhabdomyosarcoma (RMS). We report that YB-1 translocates to SGs and blocks global protein synthesis in ES, OS, and RMS cell lines that are subjected to oxidative stress or other stress forms. YB-1 knockdown (kd) dramatically reduces SG assembly under oxidative stress and renders sarcoma cells highly vulnerable to oxidative stress inducers, both of which are rescued by re-expression of YB-1 in YB-1 depleted cells. We found that G3BP1, a known SG nucleating factor, is markedly reduced in YB-1 kd cells. Mechanistically, YB-1 directly binds to IRES elements within the 5'-UTR of the *G3BP1* mRNA to activate *G3BP1* translation, thereby controlling the availability of G3BP1 for SG assembly under cell stress. YB-1 down-regulation in human sarcoma cell line xenografts significantly reduces G3BP1 levels and SG formation *in vivo* in mouse models. Notably, there is a highly significant correlation between YB-1 and G3BP1 expression across a large cohort of human sarcomas, and, like YB-1, elevated G3BP1 expression is associated with poor survival across diverse sarcomas. Together, these findings demonstrate a critical role for YB-1 in SG formation of sarcoma cells through direct translational activation of G3BP1, and suggest a link between YB-1 mediated SG formation and sarcoma progression. How this process might be blocked to render sarcoma cells more sensitive to stress induction is under intense investigation.